IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: ZHI *et al.*	Art Unit	: 1625
Serial No.	: 10/566,569	Examiner	: Seaman, D. Margaret
Filed	: August 21, 2006	Confirm. No.:	6058

Title : **6-CYCLOAMINO-2-QUINOLINONE DERIVATIVES AS ANDROGEN RECEPTOR MODULATOR COMPOUNDS**

DECLARATION PURSUANT TO 37 C.F.R. §1.132

Sir:

I, **Lin Zhi**, declare as follows,

1) I am an inventor of the above-captioned application, which claims benefit of priority to U. S. provisional patent application Serial No. 60/497,125, filed 22 August 2003.

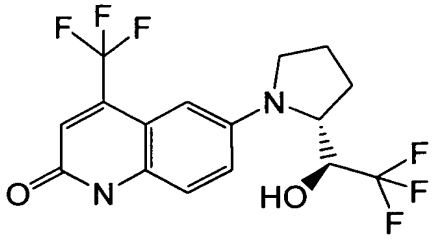
2) I obtained my B.S. and M.S. in chemistry from Beijing University in China. I obtained my Ph.D. in synthetic organic chemistry in 1990 from Emory University under the supervision of Prof. Albert Padwa. After postdoctoral training with Prof. Barry Trost in Stanford University, I joined Ligand Pharmaceuticals Inc. in 1992. I work in the area of small-molecule drug discovery targeted at intracellular/nuclear receptors. Currently, I hold the Senior Director position in Chemistry and Pharmaceutical Science at Ligand Pharmaceuticals Inc. I have over 60 publications and 60 issued US patents.

3) I have reviewed the Office Action, mailed July 28, 2009, in connection with the above-captioned application.

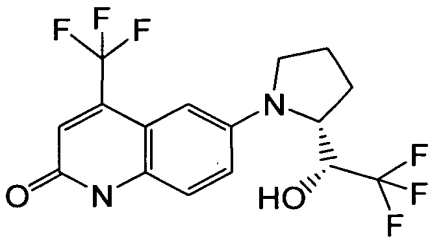
4) The above-captioned application provides selective androgen receptor modulator compounds. The compounds described in the above-captioned application interact with the androgen receptor to alter its activity.

5) I am familiar with and have reviewed the disclosure of International Pat. Appl. W02001016108 and U.S. Pat. No. 6,566,372 to Zhi *et al.* (collectively Zhi *et al*).

These references describe 595 compounds. I have reviewed these compounds and compared these compounds to the compounds of the above-captioned application, which are set forth as formula I in claim 1. Of the compounds of Zhi *et al.*, many are not structurally similar. Of the compounds that have some structural similarity, Compounds 450 and 451 described in Zhi *et al.*, which have the following structures:



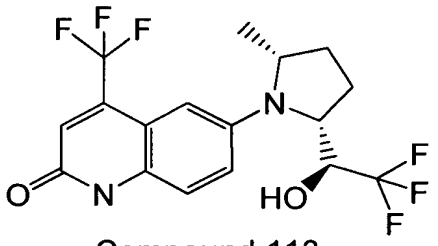
US 6,566,372
Compound 450



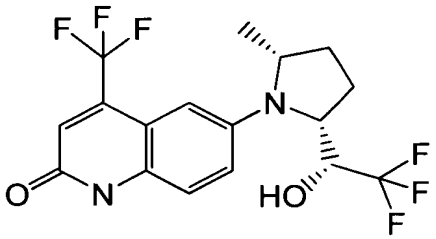
US 6,566,372
Compound 451

are most similar to compounds in the instant application. Compounds 450 and 451 of Zhi *et al.* include a single functional group on the 6-cycloamino ring – one of the carbon atoms adjacent to the nitrogen heteroatom includes only hydrogen as a substituent.

These are related to the Compounds 113 and 114 in the instant application. Compounds 113 and 114 of the instant application have the structures:



Compound 113



Compound 114

Thus, the compound described as Compound 450 in Zhi *et al.* is structurally similar to the compound described as Compound 113 of the above-captioned application. Compound 113 has a methyl group on the carbon atom adjacent to the nitrogen atom instead of a hydrogen atom.

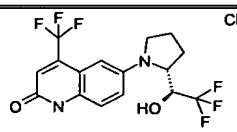
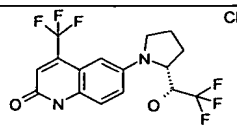
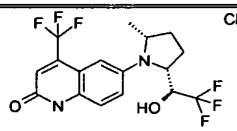
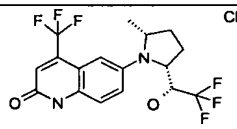
The compound described as Compound 451 of Zhi *et al.* is structurally similar to the compound described as Compound 114 of the above-captioned application, but Compound 114 has a methyl group on the carbon atom adjacent to the nitrogen atom instead of a hydrogen atom. Thus, these compounds differ from the compounds of Zhi *et al.* in that a hydrogen is replaced with a methyl.

6) I had each of Compounds 450 and 451 of Zhi *et al.* and Compounds 113 and 114 of the above-captioned application tested for genotoxicity using the standard Ames test. The Ames test assay evaluates the ability of the test compound and/or its metabolites to induce reverse mutations at the histidine locus in several strains of *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537), and at the tryptophan locus of *Escherichia coli* (*E. coli*) strain WP2*uvr*A in the presence or absence of an exogenous mammalian metabolic activation system (liver homogenate, S9). The test compounds were used in the Ames test assay at

doses of 1.00, 3.33, 10.0, 33.3, 100, 333, and 1000 μ/plate in tester strains TA98, TA100, TA1535, and TA1537 with and without S9, and at doses of 3.33, 10.0, 33.3, 100, 333, 1000, and 5000 pg/plate in tester strain WP2*uvr*A with and without S9. All doses of the test compounds, as well as the positive and vehicle controls, were evaluated in triplicate plates. The positive controls were 2-nitrofluorene for strain TA98, sodium azide for strains TA100 and TA5135, ICR-191 for strain TA1537 and 4-nitroquinoline-N oxide for WP2*uvr*A. All positive and vehicle control values were within acceptable ranges, and all criteria for a valid study were met. Liver homogenate (S9) was purchased from Molecular Toxicology, Inc. The homogenate was prepared from male Sprague-Dawley rats that had been injected (intraperitoneally) with Aroclor™ 1254 (200 mg/mL in corn oil) at 500 mg/kg, 5 days before sacrifice. Tester strains were exposed to the test compounds via the plate incorporation methodology originally described by Ames *et al.* (Mutat Res. 31(6): 347-364 (1975)) and Maron and Ames (Mutat Res. 113(3-4): 173-215 (1983)). This methodology has been shown to detect a wide range of classes of chemical mutagens. In the plate incorporation methodology, the tester strain, test compound, and S9 (where appropriate) were combined in molten top agar, which then was overlaid onto a minimal bottom agar plate. Following incubation, revertant colonies were counted (*see* Ames *et al.*, 1975). The mutant frequency is expressed as the quotient of the number of revertant colonies over the number of colonies in the negative control. A generally-accepted basic criteria for determining whether a compound is mutagenic (positive) or not (negative) are plate counts at least double the background count, and (2) a dose-related increase in plate counts. Cytotoxicity is detectable as a decrease in revertant frequency and/or a thinning or disappearance of the bacterial background lawn.

The results are shown in Table 1. In the genotoxicity assays (Ames test), the representative compounds of Zhi *et al.* (Compounds 450 and 451) were highly toxic after the compounds were treated with S9, a metabolic enzyme. In contrast, Compounds 113 and 114 of the above-captioned patent application were negative in Ames test, with or without metabolic activation, and thus, lack this toxicity. The results demonstrate the significant impact of the methyl group on the carbon atom adjacent to the nitrogen atom of the pendent heterocyclic ring on genotoxicity.

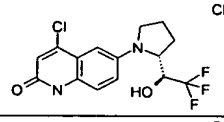
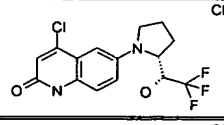
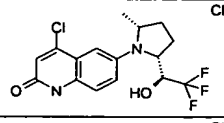
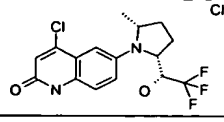
Table 1. Genotoxicity test results of representative compounds.

Compound number	Structure	Ames Test Activity
US 6,566,372 Compound 450		Strongly **positive** after S9 metabolic activation
US 6,566,372 Compound 451		Strongly **positive** after S9 metabolic activation
(122940) Compound 113		**Negative** with or without S9 activation
(122941) Compound 114		**Negative** with or without S9 activation

7) I also had 4-chloro compounds (Compounds 128-131 of the above-captioned patent application) having a secondary functional group tested in the Ames test. The results of Ames test activity are shown in Table 2. Compounds 128 and 129 are claimed in the instant application; compounds 130 and 131 are not within the scope of the claims.

Compounds 130 and 131, which lack the secondary functional group, showed strong positive activity in the Ames test after metabolic activation, while their alpha-methyl analogs (compounds 128 and 129) are totally negative in the Ames test with or without metabolic activation. Thus, Compounds 130 and 131, which lack a secondary functional group, are genotoxic after metabolic activation.

Table 2. Genotoxicity test results of 4-chloro analogs

Compound number	Structure	Ames Test Activity
Compound 130		Strongly **positive** after S9 metabolic activation
Compound 131		Strongly **positive** after S9 metabolic activation
Compound 128		**Negative** with or without S9 activation
Compound 129		**Negative** with or without S9 activation

8) Compounds 450 and 451 of Zhi *et al.* similarly do not include a secondary functional group on the 6-cycloamino ring (*e.g.*, none of the compounds include an alpha-methyl group on the 6-cycloamino ring). As described above, the compounds of Zhi *et al.* are genotoxic after metabolic activation (they showed strong positive activity in the Ames test after metabolic activation).

Compounds 113 and 114 (and all claimed compounds of formula I) of the above-captioned patent application include a secondary functional group on the 6-cycloamino ring (*e.g.*, Compounds 113 and 114 include an alpha-methyl group). The instantly claimed compounds with a secondary functional group on the 6-cycloamino ring are not genotoxic, and are totally negative in the Ames test with or without metabolic activation. 4-Chloro analogs that lack the secondary functional group showed strong positive activity in the Ames test after metabolic activation, while compounds that include the secondary functional group were totally negative in the Ames test with or without metabolic activation.

Thus, compounds of formula I of claim 1 of the above-captioned application have properties that differ from the closest compounds described in Zhi *et al.* Since the closest compounds differ substantially in toxicity, compounds that are not structurally related will have more differences in properties and activities. Further, such compounds cannot be considered homologs or structural analogs of any of the instantly claimed compounds.

Thus compounds of Zhi *et al.* are genotoxic following metabolic activation, while the compounds of formula I of claim 1 of the above-captioned application are not genotoxic, as demonstrated in the Ames test. Therefore, compounds of formula I of claim 1, which are not genotoxic, are more efficacious, *i.e.* exhibit enhanced efficacy compared to the compounds of Zhi *et al.*

9) I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

4/11/10
Date

Lin Zhi